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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/389,782	09/03/1999	COLIN R. DUNSTAN	A-604	5852
21069	7590	05/06/2005	EXAMINER	
AMGEN INC. MAIL STOP 27-4-A ONE AMGEN CENTER DRIVE THOUSAND OAKS, CA 91320-1799			HELMES, LARRY RONALD	
			ART UNIT	PAPER NUMBER
			1642	

DATE MAILED: 05/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/389,782	DUNSTAN ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 February 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21-31 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21-31 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/17/05 has been entered.
2. Claims 21-31 are pending.
Claim 21 has been amended.
3. Claims 21-31 are under examination.
4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.
5. The following Office Action contains some NEW GROUNDS of rejection.

Rejection Withdrawn

6. The rejection of claim 21 under 35 U.S.C. 102(b) as being anticipated by Boyle et al (WO 97/23614, published 7/3/97, IDS #6) is withdrawn in view of the amendments to the claim.
7. The rejection of Claims 21-31 under 35 U.S.C. 103(a) as being unpatentable over Boyle et al (WO 97/23614, published 7/3/97, IDS #6) and further in view of Mann

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et al (WO 98/28427, published 7/2/98, IDS #6) is withdrawn in view of the amendments to the claims and the new ground of rejection.

The following is a NEW GROUND of rejection/ Response to Arguments

Claim Rejections - 35 USC § 103

8. Claims 21-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boyle et al (WO 97/23614, published 7/3/97, IDS #6) and further in view of Mann et al (WO 98/28427, published 7/2/98, IDS #6).

The claims are summarized as a protein comprising an FC-OPG fusion protein wherein the Fc is a variant or fragment and the OPG comprises 22-X wherein X is from 185-193 of SEQ ID NO:2 or a variant of OPG with a deletion of one or more residues 186-401 of SEQ ID NO:2 and the protein has activity of decreasing bone resorption , further claimed is an Fc with a cysteine at position 5 deleted or substituted, and the OPG comprises residues 22-185 to 293 of SEQ ID NO:2, a linker of glycine, alanine, serine, a fusion protein comprised of SEQ ID NO:5, 6, 7, 8, polyethylene glycol polymer attached to the N-terminus and compositions comprising such. For this rejection the intended use of decreasing bone resorption recited in claim 31 is given no patentable weight.

Boyle et al teach FC-OPG fusion proteins. The fusion proteins are made up of mouse, rat, or human OPG and the fusion proteins have residues 22-X in molecules 22-

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194, 22-185, in mouse OPG. Boyle et al also teach that in human OPG residues 22-185 is required for activity (see page 25) and treatment of OPG is used to suppress the rate of bone resorption (see page 36, lines 25-27) and the mouse OPG protein is 90% identical to the human OPG amino acid sequence (see page 53, lines 22-23) and the Fc region can have a linker linking the Fc and the OPG and fusions comprising PEG and OPG wherein PEG is at the N-terminal of OPG (see pages 140-143). Boyle et al does not teach a human 22-185 or 22-194 truncated OPG fusion protein molecule, only mouse, or modification of the Fc protein or covalent attachment of PEG to the N-terminal of the Fc-OPG fusion protein or the specific sequences of SEQ ID NO:5, 6, 7, 8. These deficiencies are made up for in the teachings of Mann et al.

Mann et al teach fusion proteins comprising the Fc of SEQ ID NO:1 (see SEQ ID NO:9) and modifications to ablate the Fc receptor binding or complement binding (see page 8, lines 23-25) and many linkers, specifically the linker (Gly)₇ (see page 9, lines 10-23) and polymers conjugated to proteins and pharmaceutical compositions comprising such (see pages 15-31). Mann et al also teach the advantages of Fc fusions to proteins in general (see page 2-3) and the fusions of many proteins to Fc proteins (see pages 3-4).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the human OPG protein in substitution for the mouse OPG protein as taught by Boyle et al and produce a fusion protein with the Fc protein or a modified Fc protein or with a linker as taught by Mann et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the human in substitution for the mouse OPG protein as taught by Boyle et al and produce a fusion protein with the Fc protein with a linker as taught by Mann et al because Boyle et al specifically teaches fusion proteins of OPG to Fc (Fc-OPG) and it would have been obvious to substitute the mouse OPG for the human because Boyle et al teach the two proteins have the same activity and share 90% sequence identity and in the human OPG only residues 22-185 are needed for activity and the mouse [22-185]-Fc or mouse [22-194]-Fc were highly active and more active than the construct lacking the Fc region (see Table 1). In addition, it would have been obvious to produce a variant of the OPG human protein having a deletion of one or more residues 186-401 in the human OPG protein because the protein 22-194 of human OPG would be a variant that has the deletion and as indicated above it would have been obvious to produce such human variant. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the human OPG protein substituted for the mouse OPG protein as taught by Boyle et al and produce a fusion protein with the Fc protein with a linker as taught by Mann et al because Mann et al teach fusion proteins of Fc and many therapeutically important proteins to achieve increased circulation times and Mann et al also teach modifications to the Fc protein to ablate certain functions and fusions with a linker. It would have been obvious to substitute any therapeutically important protein such as OPG for the OB protein of Mann et al given the teachings in Boyle et al that OPG is therapeutically important for bone

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resorption. It would also be obvious to produce the fusion protein because Boyle et al teach modifications at the N or C-terminal of OPG and as such one skilled in the art would conclude that any orientation would be expected to work and in addition Boyle et al added a large polymer of PEG to the N-terminus of OPG and the OPG retained its activity (see Table 3). In addition, it would be obvious that a fusion protein of OPG and Fc with modifications as taught by Mann et al for a Fc protein and modifications as taught by Boyle et al for OPG would have the sequences recited in claim 7 and it would have been obvious that other linkers such as those recited in claim 25 can be used.


Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The response filed 2/17/05 and 7/20/04 has been carefully considered but is deemed not to be persuasive. The response of 7/20/04 states that the results obtained with the claimed Fc-OPG fusion proteins are unexpected as one skill in the art could not have anticipated that the addition of the Fc to the amino terminus of the OPG would enhance the activity and cites example 3 (see page 5-6 of the response). In response to this argument, Boyle et al clearly teach that the mouse 22-194 Fc fusion had better activity than the 22-194 alone (see Table 1) and as such one would expect the human 22-194 fusion to have a similar activity profile. In addition, one would expect the Fc-[22-194] or Fc-[22-185] of human with the Fc at the N-terminus to have an activity similar to that of the [22-194]-Fc or [22-185]-Fc because fusion of a large PEG molecule to the constructs of Boyle did not have an adverse effect on the activity.

Conclusions

9. No claims are allowed.
10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:00 am to 3:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.
11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 571-273-8300.

Larry R. Helms
571-272-0832



LARRY R. HELMS, PH.D
PRIMARY EXAMINER